HuGE Fact Sheet

Apolipoprotein E Polymorphism and Cardiovascular Disease

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Gene

Apo e is a member of the apolipoprotein gene family, a group of genes that serve a variety of functions related to lipoprotein metabolism. Apo e is located at chromosome 19q13.2 and is closely linked to the apo C-I/C-II gene complex. It consists of four exons and three introns spanning 3597 nucleotides (1). The transcript produces a 299 polypeptide (2).

Prevalence Of Gene Variants

The structural gene is polymorphic with three common alleles-- e2, e3, and e4-- that code for three isoforms of the protein, known as E2, E3, and E4. Of these variants, apo e3 shows the highest allelic frequency (> 60%) in all populations studied (3). The variants of the protein of apo E, E2, and E4, each differ from the wild type E3 by one amino acid. Crude estimates are that E2 is carried by 3%-20% of a population pool and E4 by 20%-40%, depending on the racial or ethnic heritage of the population studied (3).

Disease Burden

The apo e polymorphism has functional effects on lipoprotein metabolism mediated through the hepatic binding, uptake, and catabolism of lipid particles, i.e., chylomicrons, chylomicron remnants, very low density lipoprotein, and high density lipoprotein subspecies. Apo e contributes to variability in normal cholesterol levels in populations (3).

Interactions

The major effect of genetic variation at this locus is its influence on cholesterol levels, one of the major risk factors for cardiovascular disease (CVD), particularly coronary artery disease. With reference to cholesterol effects from the e3 allele, e4 is associated with higher total and low density lipoprotein cholesterol levels and e2 with lower levels. The cholesterol lowering effect of e2 tends to be greater than the cholesterol raising effect of e4. In total, the contribution of this gene to cholesterol variability based on a variety of populations that have been studied is no more than 10%. Diet and other genes contribute to each individual's cholesterol level, as well as to the population's average level. Many studies have looked at interactions with variants of this gene as possible modifiers of other cardiovascular risks, such as high- and low-fat diets and active vs. sedentary lifestyles. Interactions with lipid-lowering medications also have been investigated in relation to apo e. In addition, this gene has been studied as a possible risk factor for other diseases. The major finding in this regard is that one allele in particular (e4) is a risk factor for Alzheimer disease in some populations.

Laboratory Tests

Genotyping for apo e is available both for clinical purposes and for laboratory research. Several techniques have been used to determine an individual's genotype, but most involve amplification of genomic sequences containing polymorphic sites. The test is offered commercially.

Population Testing

Homozygozity for e2 has paradoxically been associated with type III hyperlipoproteinemia (1-5

per 5,000 persons) and has been used as a diagnostic criterion for this disease; however, this is a relatively rare disease, and not every e2 homozygote has this lipid disorder. When applied to screening the general population for coronary artery disease, with the exception of type III hyperlipoproteinemia, apo e genotype is not a sensitive screening test (3) . This means that it is not useful for identifying individuals with coronary artery disease. Furthermore, a high cholesterol level does not automatically mean one carries the e4 genotype, although a lower cholesterol level is more frequently associated with carriers of the e2 genotype. Individual or population screening for apo e does not give more clinically relevant information with respect to CVD than does a lipid profile.

References

1. Scott J, Knott TJ, Shaw DJ, et al. Localization of genes encoding apolipoprotein CI, CII, and E to the p13->cen region of human chromosome 19. *Hum Genet* 1985;71:144-6.

2. Rall SC, Weisgraber KH, Mahley RW. Human apolipoprotein E: the complete amino acid sequence. *J Biol Chem* 1982;257:4171-8.

3. Eichner JE, Dunn ST, Perveen G, et al. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE Review. *Am J Epidemiol* 2002;155:487-95.

Web Sites

1. National Human Genome Research Institute (NHGRI)
2. National Heart, Lung, and Blood Institute (NHLBI)
3. The Framingham Heart Study
4. Lipids Online - ApoE slides